REMARKS

I. Introduction

This paper is submitted in response to the Office action mailed January 24, 2005. A one-month extension of time for response is respectfully requested. Claims 1-34 and 36-53 are pending in the present application. Claims 1-30, 36-47 and 50-52 have been rejected. Claims 31-34, 48, 49 and 53 have been objected to. New claims 54-60 have been added to include methods of producing a chimeric RNA molecule in a cell comprising contacting the cell with a modified synthetic nucleic molecule of the present invention. No new matter has been added.

The Examiner has considered Applicants' reply filed on November 8, 2004 to traverse the restriction requirement mailed October 6, 2004. In view of Applicant's arguments the restriction requirement has been withdrawn. Applicants thank the Examiner for considering Applicants' reply and withdrawing the restriction requirement.

The Examiner states that the Specification as filed and the Declaration list the filing date of provisional application 60/008,317 as December 15, 1995, but the records of the PTO indicate the filing date is December 7, 1995. However, the present application should claim priority to provisional application 60/008,717 filed December 15, 1995, not application 60/008,317. Applicants have amended the first paragraph of the specification to correct this inadvertent error. The first paragraph of the specification has also been amended to reference the U.S. Patents that have issued since the filing date of the present application. No new matter has been added.

II. Objections to the Claims

Claims 31-34, 48, 49 and 53 have been objected to as being in improper multiple dependent form because the claims depend from other multiple dependent claims. Applicants have amended claims 31-34, 48, 49 and 53 to remove the dependency to other multiple dependent claims. Therefore, as amended claims 31-34, 48, 49 and 53 are now in conformance with 37 C.F.R. 1.75(c) and MPEP § 608.01(n).

III. The Rejections Under 35 U.S.C. §112 ¶1 Should Be Withdrawn

The Examiner has rejected claims 1-30, 36-47 and 50-52 under 35 U.S.C. 112 ¶1, alleging that the specification enables producing chimeric RNA in a cell *in vitro*, but does not enable the *in vivo* production of a chimeric RNA for therapeutic treatment.

However, "[t]he test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent and coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ 1217, 1223 (Fed. Cir. 1988). Applicants have previously published working examples of *in vivo* trans-splicing to produce a chimeric RNA, prior to the filing date of the present application (*i.e.*, February 12, 2002). In particular, PTM expression plasmids were injected into tumors of athymic (nude) mice. The tumors were established by injecting H1299 cells (human lung cancer tumors) into the dorsal flank subcutaneous space of the mouse. PTM expression plasmids were then injected into the tumors and, after 48 hours, trans-splicing was detected in 8 out of 19 PTM-treated tumors, with two of the samples producing the predicted trans-spliced product (466 bp). Six additional tumors were subsequently positive for trans-splicing, after a second PCR amplification, and again produced the predicted trans-spliced product

(196 bp). Each positive sample was sequenced, demonstrating that βHCG6 exon 1 was precisely trans-spliced to the coding sequence of DT-A (wild type or CRM mutant) at the predicted splice sites. (*See* Puttaraju *et al., Splicesome-mediated RNA trans-splicing as a Tool for Gene Therapy*, Nature Biotechnology, vol. 17, 246-52 (1999) ("Puttaraju *et al.*")). Therefore, the disclosure of the present invention would enable one skilled in the art to make or use the claimed nucleic acids and cells *in vivo*, without undue experimentation.

Moreover, an *in vitro* example in the specification constitutes a working example, sufficient to support enablement of the claimed nucleic acids and cells *in vivo*, if the example correlates with the claimed invention. Puttaraju *et al.* discloses that the mechanism of splicesome-mediated trans-splicing is the same whether it occurs *in vivo* or *in vitro*. In particular, that PTM driven trans-splicing occurred in a cell culture of human lung cancer line H1299 at the endogenously expressed βHCG6 exon 1 and the first nucleotide of DT-A, as determined *in vivo*. As a result, one skilled in the art would recognize a correlation between the results obtained using *in vitro* models and that expected *in vivo*. Therefore, Applicants respectfully submit that the *in vitro* models disclosed in specification provide sufficient evidence of *in vivo* efficacy of the present invention. (*See* MPEP 2164.02). For example, the specification discloses the successful transfer of PTMs into cells and accurate replacement of an internal exon by a double-trans-splicing between a target pre-mRNA and a PTM RNA containing both 3' and 5' splice sites leading to production of full length functionally active protein. For at least these reasons, reconsideration and withdrawal of the rejection of claims 1-30, 36-47 and

50-52 under 35 U.S.C. §112 ¶1, as failing to comply with the enablement requirement, is respectfully requested.

The Examiner has rejected claims 1-30, 36-47 and 50-52 under 35 U.S.C. 112 ¶1, as failing to comply with the written description requirement. In particular, it is alleged that the specification does not provide an adequate description of the target binding domains encompassed by the claims.

However, Applicants respectfully submit that binding domains are well known in the art and, therefore, do not need to be described in detail in the specification. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). Thus, one skilled in the art would be able to choose binding domains that target binding of the nucleic acid molecules to a pre-mRNA expressed within a cell. For example, Puttaraju et al., *Messenger RNA Repair and Restoration of Protein Function by Splicesome-Mediated RNA Trans-Splicing*, Molecular Therapy, vol. 4, 105 (2001) and Puttaraju et al., *Splicesome-mediated RNA trans-splicing as a Tool for Gene Therapy*, Nature Biotechnology, vol. 17, 246-52 (1999) disclose the testing of a number of PTMs with different binding domains, ways to test binding domains, changes that may be made to improve efficiency of a binding domain and a strategy for choosing an optimal pre-*trans*-splicing molecule (PTM). Accordingly, one skilled in the art would understand that the inventor was in possession of the claimed invention at the time of filing the application. *See, e.g., Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). Therefore, reconsideration and withdrawal of the rejection of claims 1-30, 36-47 and 50-52 under 35 U.S.C. §112 ¶1, as failing to comply with the written description requirement, is respectfully requested.

The above-mentioned references have been listed on the accompanying form PTO 1449 and copies of the articles are submitted herewith. Applicants request that the documents be considered by the Examiner and made of record in the above-referenced application.

IV. The Double Patenting Rejections Should be Withdrawn

Claims 1- 30, 36-47 and 50-52 have been rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 19-34 of U.S. Patent No. 6,013,487.

Applicants file herewith a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) to overcome the rejection based on the judicially created doctrine of double patenting, to disclaim the terminal part of the statutory term of any patent granted on the above-identified application, which would extend beyond the expiration date of U.S. Patent No. 6,013,487. Therefore, in view of the foregoing, reconsideration and withdrawal of the rejection is respectfully requested.

V. Conclusion

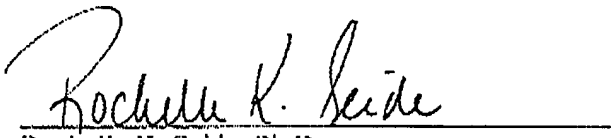
In view of the foregoing remarks and amendments, reconsideration and allowance of the pending claims is respectfully requested.

Payment of the extension fee is to be made according to the Credit Card Payment Form attached herewith. Applicants believe that no additional fees are required in connection with this response. However, if additional fees are required, the Commissioner is hereby authorized to charge any additional payment, or credit any

overpayment, to Deposit Account No. 01-2300, **referencing Docket Number**

027705.00004.

Respectfully submitted,



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